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(71) Applicant *(for all designated States except US)*: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HANSEN, John, Bondo [DK/DK]; Langåsen 3, DK-4450 Jyderup (DK).

(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).

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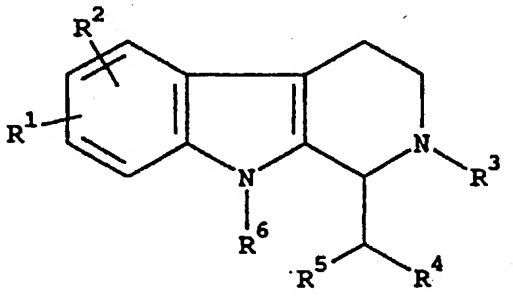
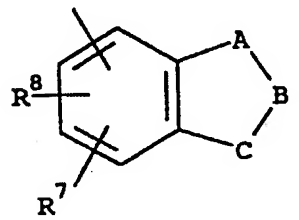
(54) Title: TETRAHYDRO-BETACARBOLINE DERIVATIVES AND THEIR PREPARATION AND USE

(57) Abstract

Tetrahydro-betacarboline derivatives of formula (I), wherein R^1 and R^2 independently are hydrogen, alkyl, cycloalkyl, alkoxy, aralkyl, halogen, halogenalkyl, nitro, alkylthio; R^3, R^5 and R^6 independently are hydrogen, alkyl, alkenyl, or cycloalkyl; and R^4 is (a), wherein A-B-C together with the benzene ring forms a five-membered heterocyclic ring comprising one or more N-, O- or S- atoms, and optionally substituted; and R^7 and R^8 independently are hydrogen, halogen, alkyl, alkenyl, nitro, CN, halogenalkyl or cycloalkyl, are useful in the treatment of disorders influenced by dysfunctions of the 5-HT_{2C} receptors.



(I)



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Tetrahydro-betacarboline Derivatives and their Preparation and Use

The present invention relates to tetrahydro-betacarboline derivatives, which binds to the 5 HT_{2C} receptor, a method of preparing the same, pharmaceutical compositions comprising the compounds, and their use in therapy , e.g. in the treatment of central and periferal nervous system disorders.

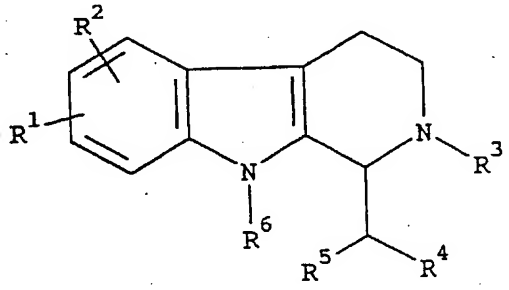
The importance of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is emphasized by the large and increasing number of known 5-HT receptors. Presently are described 5-$HT_{1A, 1B, 1D, 1E, 1F}$, 5-$HT_{2A, 2B, 2C}$, 5-HT_3, 5-HT_4, 5-$HT_{5A,5B}$, 5-HT_6, and 5-HT_7 receptors (nomenclature as agreed by the IUPHAR Committee on 5-Hydroxytryptamine Receptors). Among these receptors the 5-HT_{2A} and the 5-HT_{2C} are very similar in terms of their structure, biochemistry and pharmacology. Both receptors belong to the group of G-coupled 7-transmembrane spanning receptors and both use phosphatidylinositol hydrolysis as a second messenger system for signal transduction. The distribution and physiological role of the 5-HT_{2A} and the 5-HT_{2C}, however are markedly different and the discovery of compounds which discriminate between the two receptors is therefor of potential clinical and scientific value. Compounds which selectively modulate the 5-HT_{2C} receptor can provide treatment for the 5-HT_{2C} receptor mediated conditions without the sideeffects associated with the 5-HT_{2A}- or other receptors.

Modulators of 5-HT_{2C} receptors can be used for the treatment of diseases of the central nervous system, e.g. psychiatric and neurological

disorders, which can be schizophrenia, anxiety, depression, obsessive-compulsive disorders, panic disorders, Gilles de la Tourette syndrome, Alzheimers disease and migraine headaches. 5-HT_{2C} receptors of hypothalamus can influence sleep, appetite, thermoregulation, sexual behaviour, motor activity, and neuroendocrine function, and modulators of 5-HT_{2C} receptors can therefore be used for the treatment of e.g. sleep disorders, eating disorders and sexual dysfunction. Since 5-HT_{2C} receptors of the choriod plexus is involved in the regulation of the production of cerebrospinal fluid modulators of 5-HT_{2C} receptors can be used for the treatment of e.g. brain edema.

US 5,300,645 discloses a class of tetrahydro-betacarbolines having a 7- to 12 membered bicyclic carbon ring at the position where the compounds of the present invention have a benzene ring fused with a 5-membered heterocyclic ring. The compounds of the patent are described as modulators of 5-HT_{2C} receptors.

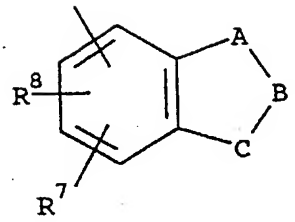
The present invention relates to tetrahydro-betacarboline derivatives of the general formula I



(I)

wherein R^1 and R^2 independently are hydrogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, aralkyl, halogen, halogenalkyl, nitro, C_{1-6}-alkylthio;
R^3, R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{3-6}-cycloalkyl; and

R^4 is



wherein A-B-C together with the benzene ring forms a five membered heterocyclic ring comprising one or more nitrogen-, oxygen- or sulphur atoms, and optionally substituted with one or more of hydrogen, halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, nitro, halogenalkyl or C_{3-6}-cycloalkyl;
R^7 and R^8 independently are hydrogen, halogen, C_{1-6}-alkyl C_{2-6}-alkenyl, nitro, CN, halogenalkyl or C_{3-6}-cycloalkyl; and
pharmaceutically acceptable salts thereof.

Physiologically and pharmaceutically acceptable salts of the compounds of the invention include acid addition salts formed with inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, nitrates, oxalates, phosphates, tartrates, citrates, fumarates, maleates, succinates, and sulphonates e.g. mesylates. If desirable, selected salts may be subjected to further purification by recrystallization.

The invention includes within its scope all optical isomers of compounds of the general formula I, some of which are optically active, and their mixtures including racemic mixtures thereof.

The term "C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1-6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.butyl, n-pentyl, neopentyl, n-hexyl, 2,2-dimethylpropyl.

The term "C_{3-6}-cycloalkyl" as used herein denotes a saturated monocyclic hydrocarbon having 3-6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen, e.g. methoxy, ethoxy, propoxy, isopropoxy, cyclopropylmethoxy, butoxy, pentoxy.

The term "aralkyl" as used herein, alone or in combination, refers to an alkyl chain of 1 to 6 carbon atoms substituted with phenyl or naphthyl. Examples of such aralkyl groups are benzyl, phenethyl, 1-naphthylmethyl.

The term "halogen" as used herein means fluorine, chlorine, bromine and iodine.

The term "halogenalkyl" as used herein, refers to an alkyl group as defined above containing one or more halogen atoms replacing some or all of the hydrogens thereon, e.g. trifluoromethyl, trifluoroethyl, trichloromethyl, trichloroethyl, tribromomethyl.

The term "C_{1-6}-alkylthio" as used herein, refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through sulfur, e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio.

The term "C_{2-6}-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6 carbon atoms and one double bond such as vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

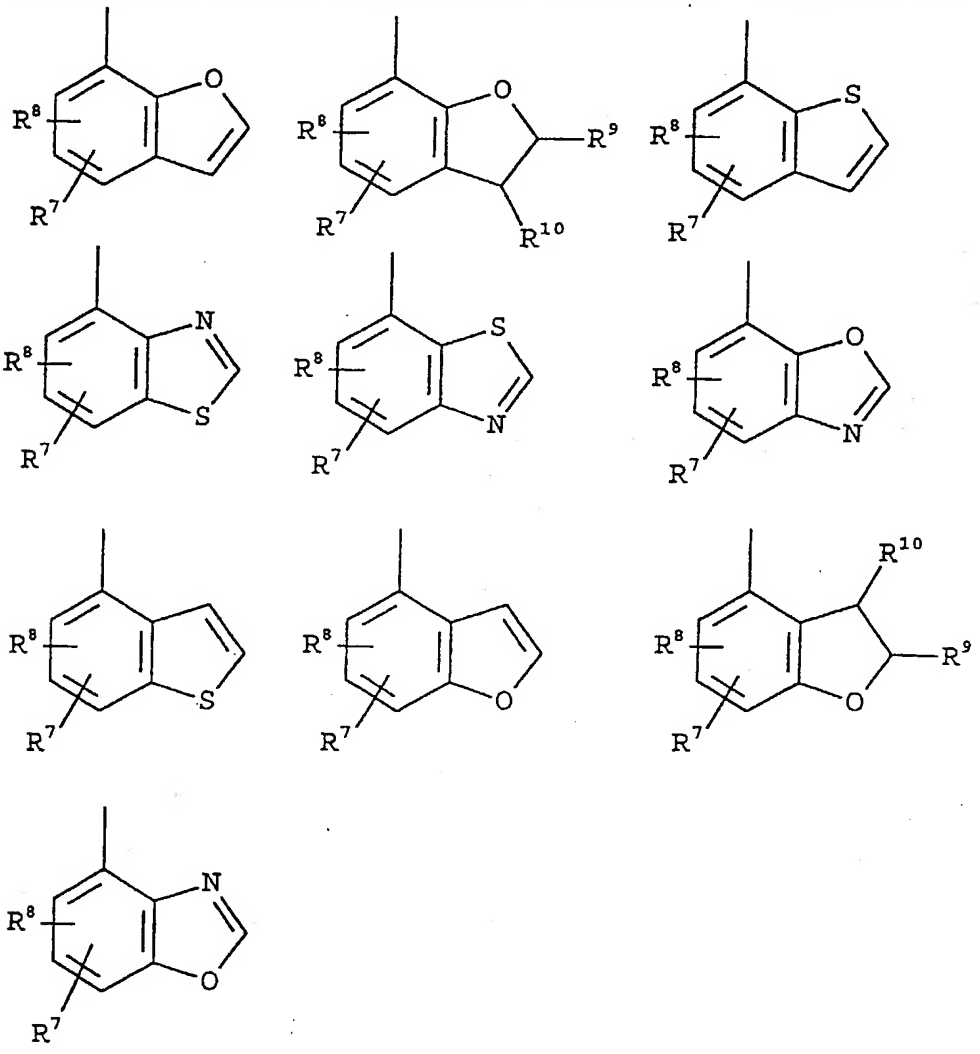
The term "five membered heterocyclic ring" as used herein refers to a

ring containing one or more hetero atoms selected from nitrogen, oxygen and sulphur and having five members, e.g. furan, thiophene, pyrrole, imidazole, isoxazole, isothiazole, thiazole, 2,3-dihydrofuran, 2,3-dihydro-thiophene.

In a preferred embodiment of the invention R^1 and R^2 are selected from chlorine, bromine, methyl and isopropyl.

In another preferred embodiment of the invention R^3, R^5 and R^6 are selected from hydrogen, methyl and allyl.

In yet another preferred embodiment of the invention R^4 is selected from:



wherein R^7, R^8, R^9 and R^{10} independently are hydrogen, halogen, C_{1-6}-alkyl, nitro, CN or triflouromethyl.

Preferred compounds of the invention are:

1-(7-Benzofuranylmethyl)-1,2,3,4-tetrahydro-betacarboline, hydrochloride;
1-(7-Benzofuranylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline, hydrochloride;
1-(7-Benzofuranylmethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline, hydrochloride;
1-(2,3-Dihydrobenzofuran-7-ylmethyl)-1,2,3,4-tetrahydro-betacarboline, oxalate.

Other preferred compounds of the invention are:

1-(7-Benzofuranylmethyl)-1,2,3,4-tetrahydro-betacarboline;
1-(7-Benzofuranylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;
1-(2,3-Dihydrobenzofuran-7-ylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;
1-(1-(7-Benzofuranyl)ethyl)-1,2,3,4-tetrahydro-betacarboline;
1-(1-(7-Benzofuranyl)ethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;
1-(1-(2,3-Dihydrobenzofuran-7-yl)ethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;
1-(1-(2,3-Dihydrobenzofuran-7-yl)ethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline;
1-(1-(2,3-Dihydrobenzofuran-7-yl)ethyl)-6-isopropyl-1,2,3,4-tetrahydro-betacarboline;
1-(5-Bromo-benzofuran-7-ylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;
1-(5-Chloro-benzofuran-7-ylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;

1-(5-Chloro-benzofuran-7-ylmethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline;

1-(5-Bromo-benzofuran-7-ylmethyl)-6-isopropyl-1,2,3,4-tetrahydro-betacarboline;

1-(5-Bromo-benzofuran-7-ylmethyl)-6-isopropyl-9-methyl-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzothienylmethyl)-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzothienylmethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzothienylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;

1-(1-(7-Benzothienyl)ethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;

1-(1-(7-Benzothienyl)ethyl)-6-isopropyl-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzoxazolylmethyl)-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzoxazolylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzoxazolylmethyl)-6-isopropyl-1,2,3,4-tetrahydro-betacarboline;

1-(7-Benzoxazolylmethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline;

1-(1-(7-Benzoxazolyl)ethyl)-1,2,3,4-tetrahydro-betacarboline;

1-(1-(7-Benzoxazolyl)ethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline;

1-(1-(7-Benzoxazolyl)ethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline;

1-(1-(7-Benzoxazolyl)ethyl)-6-isopropyl-1,2,3,4-tetrahydro-betacarboline;

or pharmaceutically acceptable acid addition salts of these compounds.

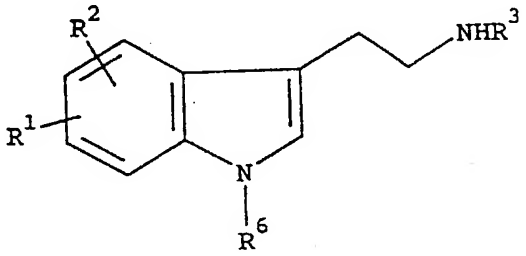
The compounds of the present invention demonstrate high affinity for the $5HT_{2c}$ receptor.

Accordingly, in another aspect the invention relates to a compound of the general formula (I) or a pharmaceutically acceptable acid addition salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of diseases of the central nervous system, sleep disorders, eating disorders or sexual dysfunctions, all influenced by dysfunctions of the $5HT_{2c}$ receptors.

Furthermore, the invention also relates to the use of the inventive compounds of formula (I) as medicaments useful for treating diseases of the central nervous system, e.g. psychiatric and neurological disorders, which can be schizophrenia, anxiety, depression, obsessive-compulsive disorders, panic disorders and further diseases related to sleep, appetite, thermoregulation, sexual behaviour, motor activity and neuroendochine function e.g. sleep disorders, eating disorders, sexual dysfunctions or for treating brain edema.

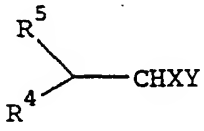
In yet another aspect, the invention relates to methods of preparing the above mentioned compounds. These methods comprise:

a) reacting a compound of formula II



(II)

wherein R^1, R^2, R^3 and R^6 are as defined above, with a compound selected from III or IV



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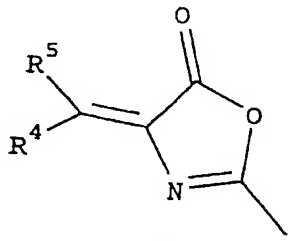
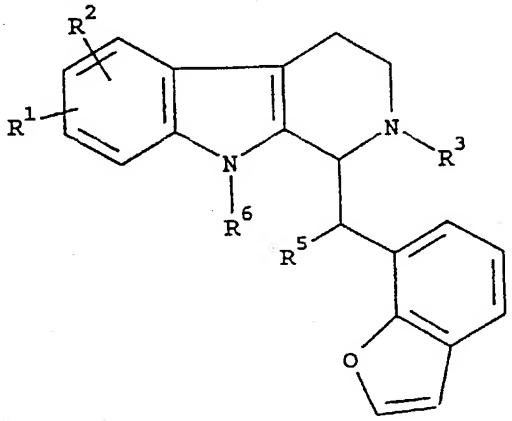


(IV)

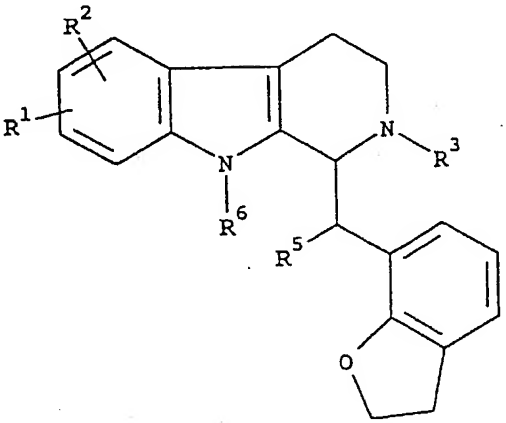
wherein R^4 and R^5 are as defined above and CHXY forms an aldehyde or a derivatives thereof capable of reacting like an aldehyde, to form a compound of formula I;

b) treating a compound of formula V



(V)

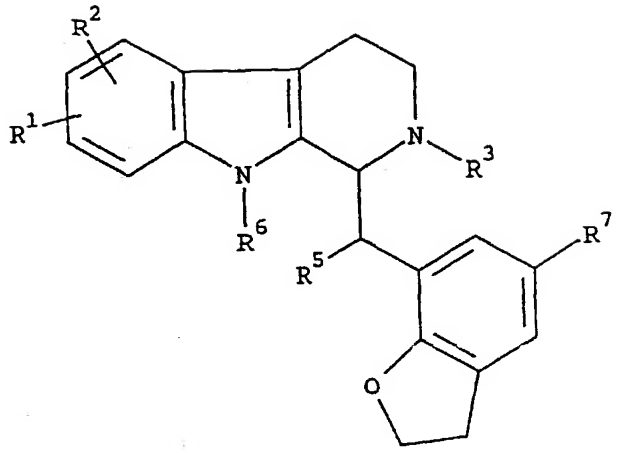
wherein R^1, R^2, R^3, R^5 and R^6 are as defined above, with hydrogen in the presence of a catalyst, which can be Pd or Rh on activated carbon , PtO_2 or RaNi, to form a compound of formula VI



(VI)

wherein R^1, R^2, R^3, R^5 and R^6 are as defined above;

c) treating a compound of formula VI with an electrophile reagent, by a method described in e.g. J March, Advanced Organic Chemistry, 4. Ed. (1992), to form a compound of formula VII



(VII)

wherein R^1, R^2, R^3, R^5, R^6 and R^7 are as defined above.

The compounds of the present invention have been tested for their affinity for the $5HT_{2c}$ receptor.

The affinity for the $5HT_{2c}$ receptor may be determined by radioligand binding assays using ^{3}[H]-Mesulergine as determined in D. Hoyer, *J. Receptor. Res.* 8, 59-81, (1988); D. Hoyer et al, *Eur. J. Pharmacol.* 118, 13-23, (1985); K. D. Bunis et al, *J. Pharm. Exp. Ther.* 258, 891-896, (1991).

The $5HT_{2c}$ receptor affinity, as determined by IC_{50} values were typically in the range of 1nM to 1μM.

The compounds of the invention, together with a conventional adjuvant, carrier or diluent, and if desired a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs or capsules filled with the same, all for oral use; in the form of suppositories for rectal administration, or in the

form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing 0.05-500 mg of active ingredient, more specified 0.1-200 mg or especially 1-100 mg per tablet are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations e.g. for oral and parenteral administration to mammals including humans in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or oral application which do not deleteriously react with the active compound.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compound.

For parenteral application, particularly suitable are injectable solutions or

suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

For oral applications, particularly suitable are tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or like can be used when a sweetened vehicle can be employed. Generally, as to broader ranges, the compound of the invention is dispensed in unit dosage form comprising 0.05-500 mg, more specified 0.1-200 mg or especially 1-100 mg, in a pharmaceutically acceptable carrier per unit dosage.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	1.0 mg
Lactosum	67.9 mg Ph.Eur
Avicel®	31.4 mg
Amberlite® IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

The following non-limitating examples illustrate the invention.

EXAMPLE 1

1-(7-Benzofuranyl)-1,2,3,4-tetrahydro-betacarboline, hydrochloride

Benzofuran-7-carbaldehyde (12.1 g, 83 mmol), N-acetylglycine (9.7 g. 83 mmol), sodium acetate (11.28 g, 83 mmol) and acetic anhydride (100 ml) was stirred at 100°C for 8 hours. The mixture was then cooled

to room temperature and poured onto ice. A yellow precipitate was isolated, washed with water and ether and dried to give 10.2 g of 4-(7-benzofuranylmethylene)-2-methyloxazol-5-one M.p. 172.1-173.5°C.

4-(7-benzofuranylmethylene)-2-methyloxazol-5-one (6.8 g, 30 mmol) and tryptamine, hydrochloride (3.2 g, 20 mmol) in 200 ml 1 N HCl was refluxed under nitrogen for 20 hours. The mixture was then cooled to 0°C, whereupon the formed precipitate was isolated and washed with 1 N HCl, water, 2-propanol and ether to give 6.8 g of the title compound.

A sample of this product was additionally purified by separation between ethyl acetate and 2 N NaOH. The organic phase was washed with water and saturated sodium chloride, dried over sodium sulfate and concentrated in vacuo. The resulting oil was taken up in ethanol and hydrogen chloride in ether added to crystallize the title compound. M.p. 240-241°C.

EXAMPLE 2

1-(7-Benzofuranylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline, hydrochloride

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4-(7-benzofuranylmethylene)-2-methyloxazol-5-one (1.6 g, 7 mmol) and 5-methyltryptamine, HCl (1 g, 4.7 mmol) was refluxed in 25 ml 1 N HCl for 24 hours. The mixture was then cooled to 0°C and filtered to isolate a semicrystalline brown precipitate which was washed with 2-propanol and recrystallized from ethanol to give 120 mg of the title compound. M.p. > 240°C.

EXAMPLE 3

1-(7-Benzofuranylmethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline, hydrochloride

Starting from 4-(7-benzofuranylmethylene)-2-methyloxazol-5-one (1.6 g, 7 mmol) and 5-chlorotryptamine, HCl (1.2 g, 5 mmol) the title compound was prepared by the procedure described in example 1 to give 450 mg of the title compound. M.p. > 230°C.

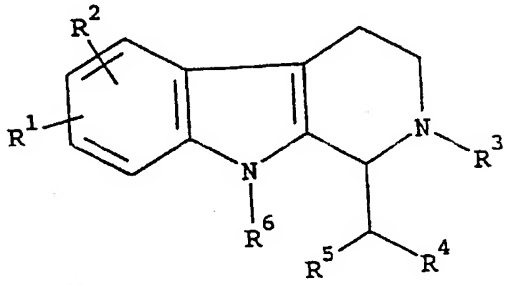
EXAMPLE 4

1-(2,3-Dihydrobenzofuran-7-ylmethyl)-1,2,3,4-tetrahydro-betacarboline, oxalate

1-(7-Benzofuranyl)-1,2,3,4-tetrahydro-betacarboline (0.8 g, 2.6 mmol) was dissolved in 50 ml glacial acetic acid and reduced catalytically using 100 mg 5% Pd on carbon (RT, 30 psi). The mixture was filtered and separated between CH_2Cl_2 and aqueous potassium carbonate (PH = 8). The organic phase was dried over magnesium sulfate and concentrated in vacuo to get 500 mg oil, which was taken up in 2 ml dry acetone. 200 mg oxalic acid was added to precipitate the desired compound. Recrystallization from acetone and ethanol gave 400 mg of the title compound. M.p. 235-238°C.

CLAIMS

1. A compound of the general formula (I)

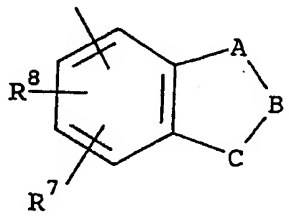


(I)

wherein R^1 and R^2 independently are hydrogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, aralkyl, halogen, halogenalkyl, nitro, C_{1-6}-alkylthio;

R^3, R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{3-6}-cycloalkyl; and

R^4 is



wherein A-B-C together with the benzene ring forms a five membered heterocyclic ring comprising one or more nitrogen-, oxygen- or sulphur atoms, and optionally substituted with one or more of hydrogen, halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, nitro, halogenalkyl or C_{3-6}-cycloalkyl;

R^7 and R^8 independently are hydrogen, halogen, C_{1-6}-alkyl C_{2-6}-alkenyl, nitro, CN, halogenalkyl or C_{3-6}-cycloalkyl; and

pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R^1 and R^2 are selected from chlorine, bromine, methyl and isopropyl.

3. A compound according to claim 1 wherein R^3, R^5 and R^6 are selected from hydrogen, methyl and allyl.

4. A compound according to any of the claims 1-3 wherein R^4 is selected from benzofuranyl, 2,3-dihydrobenzofuranyl, 5-bromo-2,3-dihydrobenzofuranyl, 5-chloro-2,3-dihydrobenzofuranyl, 5,6-dichloro-2,3-dihydrobenzofuranyl, benzothienyl, 2,3-dihydrobenzothienyl, benzimidazolyl, 1,2-benzisoxazolyl, benzthiazolyl and benzoxazolyl.

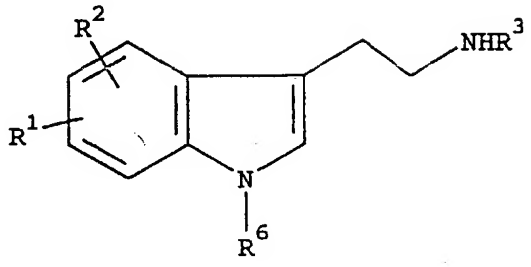
5. A compound according to any of the claims 1-4 which is
1-(7-Benzofuranylmethyl)-1,2,3,4-tetrahydro-betacarboline, hydrochloride,
1-(7-Benzofuranylmethyl)-6-methyl-1,2,3,4-tetrahydro-betacarboline, hydrochloride,
1-(7-Benzofuranylmethyl)-6-chloro-1,2,3,4-tetrahydro-betacarboline, hydrochloride;
1-(2,3-Dihydrobenzofuran-7-ylmethyl)-1,2,3,4-tetrahydro-betacarboline, oxalate.

6. A compound according to any of the claims 1-5 or a pharmaceutically acceptable salt thereof for use as a therapeutically acceptable substance.

7. A compound according to any of the claims 1-5 or a pharmaceutically acceptable salt thereof for use as a therapeutically acceptable substance in the treatment of central nervous system disorders, sleep disorders, eating disorders and sexual dysfunctions, all influenced by dysfunction of the 5-HT_{2c} receptors.

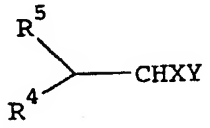
8. A method of preparing a compound according to any of the claims 1-5, which comprises:

a) reacting a compound of formula II

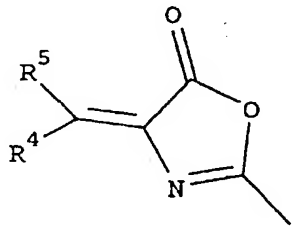


(II)

wherein R^1, R^2, R^3 and R^6 are as defined above with a compound selected from III or IV



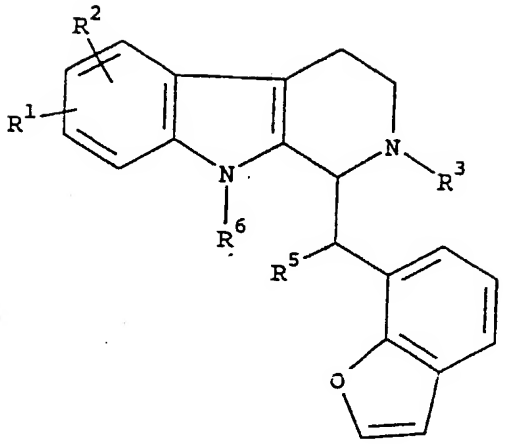
(III)



(IV)

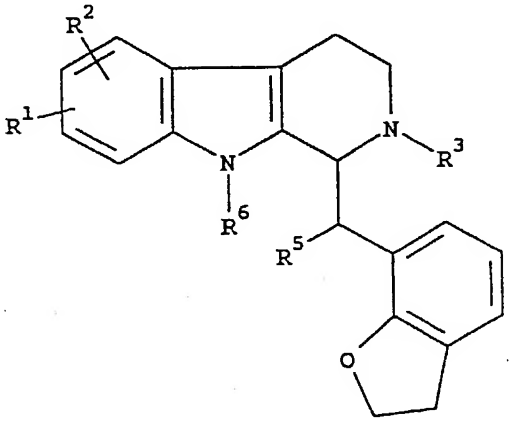
wherein R^4 and R^5 are as defined above and CHXY forms an aldehyde or a derivatives thereof capable of reacting like an aldehyde, to form a compound of formula I;

b) treating a compound of formula V



(V)

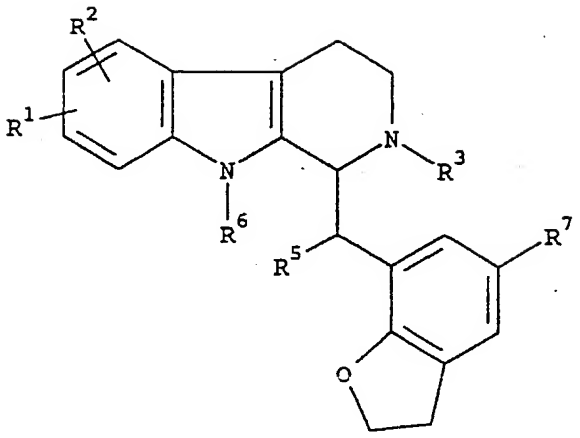
wherein R^1, R^2, R^3, R^5 and R^6 are as defined above, with hydrogen in the presence of a catalyst, which can be Pd or Rh on activated carbon , PtO_2 or RaNi, to form a compound of formula VI



(VI)

wherein R^1, R^2, R^3, R^5 and R^6 are as defined above;

c) treating a compound of formula VI with an electrophile reagent, by a method described in e.g. J March, Advanced Organic Chemistry, 4. Ed. (1992), to form a compound of formula VII



(VII)

wherein R^1, R^2, R^3, R^5, R^6 and R^7 are as defined above.

9. A pharmaceutical composition comprising a compound according to any of the claims 1-5 or a pharmaceutically acceptable salt thereof, and a therapeutically inert excipient, carrier or diluent.

10. A pharmaceutical composition for the treatment of central nervous system disorders, sleep disorders, eating disorders and sexual dysfunctions, all influenced by dysfunctions of the $5HT_{2C}$ receptors, which composition comprises a compound according to any of the claims 1-5 or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient, carrier or diluent.

11. Use of a compound according to any of the claims 1-5 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the treatment of central nervous system disorders, sleep disorders, eating disorders and sexual dysfunctions, all influenced by dysfunction of the $5\text{-}HT_{2C}$ receptors.

12. A method of treating central nervous system disorders, sleep disorders, eating disorders and sexual dysfunctions, all influenced by dysfunction of the $5\text{-}HT_{2C}$ receptors in a subject in need thereof com-

prising administering an effective amount of a compound according to any of the claims 1-5.

13. A method of treating central nervous system disorders, sleep disorders, eating disorders and sexual dysfunctions, all influenced by dysfunction of the 5-HT_{2C} receptors in a subject in need thereof comprising administering a pharmaceutical composition according to claim 9.

14. A process for the manufacture of a pharmaceutical composition to be used in the treatment of central nervous system disorders, sleep disorders, eating disorders and sexual dysfunctions, all influenced by dysfunction of the 5-HT_{2C} receptors, which process comprising bringing a compound of formula I according to claim 1 and a pharmaceutically acceptable salt thereof into a galenical dosage form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00258

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/04, A61K 31/475
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 51, No 4, 25 February 1957 (25.02.57), (Columbus, Ohio, USA), Masayuki Onda et al, "Analogs of Rauwolfia alkaloids. III. Syntheses of 1-substituted tetrahydro-beta-carbolines and hexadehydroyohimbans", THE ABSTRACT No 2824f, J. Pharm. Soc.Japan 1957, 76, 966-968	1,3
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A	US 5300645 A (JAMES E. AUDIA ET AL), 5 April 1994 (05.04.94)	1-11,14
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A	GB 1506982 A (ROUSSEL - UCLAF), 12 April 1978 (12.04.78)	1-11,14
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 Sept 1996	11 -10- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00258

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-13
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/09/96

International application No.
PCT/DK 96/00258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5300645	05/04/94	AU-A- 6705294	08/11/94
		CA-A- 2160480	27/10/94
		EP-A- 0620223	19/10/94
		US-A- 5488053	30/01/96
		US-A- 5538980	23/07/96
		US-A- 5538981	23/07/96
		WO-A- 9424132	27/10/94
		ZA-A- 9402544	13/10/95
GB-A- 1506982	12/04/78	BE-A- 840610	11/10/76
		CH-A- 609983	30/03/79
		DE-A- 2615623	21/10/76
		FR-A,B- 2306693	05/11/76
		JP-A- 51122097	25/10/76
		LU-A- 74744	04/02/77
		NL-A- 7603770	13/10/76